consider an amendment whereby the claims were limited to GLP analogs which differ from the wild type sequence by virtue of a single amino acid substitution at position 8.

Election of Species

The Examiner required Applicants to elect a disclosed species. In response to this requirement, Applicants hereby elect Val^8-GLP-1 (7-37)OH. Claims that read on this species are Claims 1-15, 18-19, 21-23, 25-33 and 35-43.

Claim Amendments and Support For The Amendments

For the convenience of the Examiner, a copy of the claims which are pending in this application, as amended by this Paper, is included herewith.

A. Claims 1, 21 and 31

Claims 1, 21 and 31 have been amended so that the GLP-1 molecules are limited to analogs of GLP-1 (7-37)OH and GLP-1 (7-36)NH_2 in which alanine at position 8 has been replaced with Gly, Val, Thr, Ile and alpha-methyl-Ala. Support for this amendment is found on page 9, lines 1-17 of the specification. These lines disclose SEQ ID NO: 1, which has variables at positions 7, 8, 21 and 27. Lines 11-12 on page 9 recite Gly, Val, Thr, Ile and alpha-methyl-Ala as possible values for position 8, as recited in Claims 1, 21 and 31.

It is noted further that Claims 1, 21 and 31 require position 7 to be histidine and positions 21 and 27 to be glutamic acid. Support for this limitation is also provided on page 9, lines 1-17, which provides histidine as a possible amino acid at position 7 of SEQ ID NO: 1 and glutamic acid a possible amino acid at position 21 and 27 of SEQ ID NO: 1.

Claims 1, 21 and 31 have also been amended to more clearly define the invention.

B. Claim 2 and Claims 18-19, 23 and 33

Claim 2 has been amended to correct a typographical error.

Claims 18-19, 23 and 33 have been amended to convert the claims into independent format.

C. Claims 42-44

Claims 42-44 have added and recite GLP-1(7-34)OH, GLP-1(7-35)OH, GLP-1(7-36)OH, GLP-1(7-37)OH and the amide form thereof, all having an amino acid residue with an uncharged side chain at position 8 in place of alanine.

Applicants respectfully submit that there is adequate written description in the specification to support new Claims 41-43, even though language used in these claims is not literally recited in the specification. It is well established in U.S. Patent Law that the first paragraph of 35 U.S.C. § 112 can be satisfied, even if the specification does not literally recite the claim language:

> We cannot agree with the broad proposition, apparent in the above-quoted language, that in every case where the description of the invention in the specification is narrower than in the claim there has been a failure to fulfill the description requirement in section 112. Each case must be decided on its own facts. *In re Smythe and Shamos,* 178 USPQ 279, 284 (CCPA, 1973).

The test for sufficiency of support in a patent application is whether the disclosure reasonably conveys the invention to one of ordinary skill in the art:

> Does the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound claimed. *Vas-Cath, Inc. v. Marurkar,* 12 USPQ2d 1111, 1115 (CAFC, 1991), quoting *In re Ruschig,* 154 USPQ 118 (CCPA, 1967).

It is not necessary that a specification disclose the boundaries of a claim limitation when one of ordinary skill in the art would readily understand what is encompassed by the claim limitation:

> We do not agree that because the reissue claims would encompass differing tip shapes, each such tip shape must be disclosed before Peters may be given the benefit of §251.
>
> Nor do we agree that the disclosed tip configuration was critical. No prior art was distinguished from and no rejection was overcome on the basis of the tip shape. Most importantly, one skilled in the art would readily understand that in practicing the invention it is unimportant whether the tips are tapered, and the board erred in determining the contrary.
>
> ...The broadened claims merely omit an unnecessary limitation that had restricted one element of the invention to the exact and non-critical shape disclosed in the original patent. In sum, nothing in the original disclosure indicates or suggests that the tapered shape was essential or critical to either the operation or patentability of the invention. *In re Peters and Anderson,* 221 USPQ 952, 953 (CAFC, 1983).

One of ordinary skill in the art would readily understand that Applicants had in hand the inventions recited in Claims 41-43. Therefore, Claims 41-43 satisfy the written description requirement of Section 112. Support for this position is provided in the following paragraphs.

The subject specification describes GLP-1 molecules of varying length. For example, GLP-1(7-34)OH through GLP-1(7-37)OH and the *C*-terminal amide form of these molecules is described on page 9, lines 18-25. The specification also describes the replacement of alanine at position 8 in these molecules with amino acid residues having non-charged side-chains, specifically glycine, cysteine and serine (see page 9, lines 18-25 taken together with page 10, lines 12-13).

The subject specification discloses a large number of other examples of amino acid residues with non-charged side chains which can substitute for alanine at position 8 of

GLP-1 molecules. Examples include glycine, valine, threonine, isoleucine and alpha-methyl alanine for GLP-1(7-37)OH and GLP-1(7-36)NH_2 (page 9, lines 11-12); and Gly^8 GLP-1(7-36)NH_2, alpha-methyl $alanine^8$ GLP-1(7-36)NH_2 and Val^8 GLP-1(7-37)OH (page 11, lines 4-6). Therefore, the subject application clearly contemplates the replacement of alanine at position 8 of molecules GLP-1(7-34)OH through GLP-1(7-37)OH, including the *C*-terminal amide form thereof, with non-charged amino acids other than those specifically recited in the prior paragraph.

In summation, the specification describes GLP molecules of varying length (7-34 through 7-37) and *C*-terminal amide forms thereof, along with a wide range of suitable amino acids having non-charged side chains which can substitute for alanine at position 8 of GLP molecules. This description clearly conveys to one of ordinary skill in the art that Applicants had this genus in their possession at the time the subject application was filed.

Rejection of Claims 1-17, 21, 22, 25-32 and 35-40 under 35 USC 112, First Paragraph

Claims 1-17, 21, 22, 25-32 and 35-40 are rejected as not being enabled by the specification. The Examiner stated that Applicants have not established that any and all peptides covered by the claims will be effective whether administered by inhalation, intraveneous, injection or other means.

Applicants respectfully disagree with the Examiner's assertion that the effectiveness of GLP molecules has not been established. In fact, the use of a wide variety of GLP molecules, analogs and derivatives to treat diabetes is well known. Support for this position is provided by US Patent Nos. 5,545,618, 5,977,071 and 5,705,483, which are included herewith as Exhibits A, B and C, respectively (see the Abstract of Exhibit A; the Abstract, Example 1 and Claims 1 and 7 of Exhibit B; and the Abstract, Example 1 and the claims of Exhibit C). Particular note is made of the Claim 1 of

Exhibit C, which is drawn to valine^{8}-GLP(7-37)OH.

Applicants' invention differs from the disclosure of Exhibits A-C in that Applicants' invention is directed to pulmonary delivery, e.g., inhalation, of certain GLP molecules. The teachings of Exhibits A-C are limited to administering GLP molecules parenterally, orally, by injection or by transmembrane or transdermal means (first paragraph of column 14 in Exhibit A; column 10, lines 29-37 of Exhibits B; and column 10, lines 23-30 of Exhibit C). These references therefore do not provide any expectation that pulmonary delivery would be successful in providing sufficient bioavailability to be therapeutically effective. In fact, it is well established that pulmonary delivery of small peptides (peptides less than about 30 amino acids) is generally ineffective because such peptides are often degraded by proteases in the lungs. Support for this assertion is provided by Patton *et al. Pulmonary Absorbtion and Metablism of Peptides and Proteins* in "Respiratory Drug Delivery VI", Interpharm Press, Buffalo Grove, IL, editors RN Dalby, PR Byron and SJ Farr (1998) and Byron *et al. Journal of Aerosol Medicine* 7:49 (1994), which are enclosed herewith as Exhibits D and E (see the Summary and the first paragraph of Exhibit D and the last paragraph on page 57 of Exhibit E).

Based on the teachings of Exhibits D and E, the skilled person would expect pulmonary delivery of GLP molecules to be therapeutically ineffective. It would be expected that GLP molecules, which consist of 31 amino acids or less, would be degraded by proteases in the lungs. Applicants have overcome the problem of protease degradation by selecting GLP molecules which are resistant to degradation by dipeptidyl-peptidase IV (DPP IV). Valine^{8}-GLP-1(7-37)OH, which is encompassed by the Claims 1-15, 18-19, 21-23, 25-33 and 35-43, is an example of a DPP IV resistant peptide. Support for the assertion that valine^{8}-GLP-1(7-37)OH is DPP IV resistant is provided in column 3, lines 42-57 of US Patent No.

5,705,483 (Exhibit C), which has claims (1-4) drawn to valine^{8}-GLP-1(7-37)OH.

Support for the assertion that Applicants have overcome the problem of protease degradation in the lungs is provided in the Example of the subject application (pages 24-34). Specifically, the Example shows that valine^{8}-GLP-1(7-37)OH has good bioavailability when administered by pulmonary means to beagle dogs (page 26, lines 5-11). Based on deposited lung dose, the bioavailability of valine^{8}-GLP-1(7-37)OH relative to subcutaneous injection was 40% (page 34, lines 11-16). In addition, the absorption and plasma time profiles for valine^{8}-GLP-1(7-37)OH administered by pulmonary means and valine^{8}-GLP-1(7-37)OH administered by subcutaneous injection were found to be similar (page 34, lines 1-10).

As noted above, the efficacy of valine^{8}-GLP-1(7-37)OH in normalizing blood glucose levels when administered parenterally has already been established in US Patent No. 5,705,483 (see the Abstract, Example 1, column 10, lines 25-36 and Claims 1-4 of Exhibit C). The teachings of US Patent No. 5,705,483 taken together with the evidence, summarized in the previous paragraph, showing good bioavailability for valine^{8}-GLP-1(7-37)OH when delivered by pulmonary means demonstrates that pulmonary delivery of valine^{8}-GLP-1(7-37) is therapeutically effective.

Having demonstrated that valine^{8}-GLP-1(7-37)OH is bioavailable and therefore effective when delivered by pulmonary means, the skilled person would expect that closely related DPP IV resistant analogs would also be therapeutically effective. The lack of any rejection by the Examiner of Claims 18 and 19, which recite delivering Gly^{8}-GLP-1(7-37)OH and Asp^{8}-GLP-1(7-37)OH by pulmonary means, is consistent with this position.

The GLP molecules recited in amended Claims 1, 18, 21, 31 and 41-43 are DPP IV resistant analogs of valine^{8}-GLP-1(7-37)OH and differ from valine^{8}-GLP-1(7-

37)OH by length and/or by virtue of a conservative amino acid substitution at position eight. Specifically, valine at position 8 is replaced with an amino acid having a non-charged side chain. It is well established that replacing alanine at position 8 with an amino acid having a non-charged side chain results in a DPP IV resistant peptide that retains biological activity. Support for this assertion is provided by Deacon *et al.*, *Diabetologia 41:*271 (1998) and Ritzel *et al.*, *J. of Endocrinology 159:*93 (1998), enclosed herewith as Exhibits F and G, respectively (see the Abstract of Exhibits F and G). Based on their resistance to DPP IV degradation, one of ordinary skill in the art would expect that these variants would be therapeutically effective when delivered by pulmonary means.

In summation, amended Claims 1-17, 21, 22, 25-32 and 35-40, which are directed to administering certain GLP molecules by pulmonary means, are enabled by the specification. The therapeutic benefit of GLP molecules when administered by traditional routes (e.g., parenterally) is well established by the prior art. The Example in the subject specification demonstrates the bioavailability of Val^8-GLP-1(7-37)OH when delivered by pulmonary means. This evidence, taken together, shows that pulmonary administration of this molecule is therapeutically effective. The good bioavailability of Val^8-GLP-1(7-37)OH is believed to be due to the fact that it is resistant to degradation by DPP-IV. One of ordinary skill in the art would therefore expect that structural analogs of Val^8-GLP-1(7-37)OH which are DPP IV resistant, such as those recited in the amended claims, would also be bioavailable after pulmonary administration and therefore have a beneficial therapeutic effect when administered by this route. This position is consistent with the fact that Claims 18 and 19 were not rejected under 35 USC 112, first paragraph.

SUMMARY AND CONCLUSION

In view of the remarks and amendments provided herein above, it is respectfully submitted that the rejections under 35 U.S.C. 112, first paragraph have been overcome. Reconsideration and withdrawal of the rejection are therefore requested.

If the Examiner feels that a telephone conversation with Applicants' Attorney would be helpful in expediting the prosecution of this case, the Examiner is urged to call Applicants' Attorney at (617) 250-1833.

Respectfully submitted,

Steven G. Davis
Attorney/Agent for
Applicants

Registration No. 39,652
Phone: 617-250-1833

Eli Lilly and Company
Patent Division/SGD
Lilly Corporate Center
Indianapolis, IN 46285

March 30, 2000
Date